Exhibit I

REVIEW ARTICLE

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Medication-Induced Intracranial Hypertension in Dermatology

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Contents

Abstract

Pseudotumor cerebri (PTC) is a syndrome of intracranial hypertension that is idiopathic or from an identified secondary cause. It is characterized by headaches and visual manifestations. The hallmark of PTC is papilledema and the feared consequence is visual loss that may be severe and permanent. The idiopathic form generally occurs in obese women of childbearing age.

Various medications may produce PTC in patients at any age, including children. Several medications used in dermatology, particularly those used in the treatment of acne vulgaris, are associated with PTC. There is a strong association with tetracycline usage. Minocycline and doxycycline have also been linked to PTC, although there are relatively few reported cases. PTC has also been described with retinoids, including vitamin A (retinol) and isotretinoin. Although corticosteroids are often used to lower intracranial pressure acutely, corticosteroid withdrawal after long-term administration may induce increased intracranial pressure. A high index of suspicion, early diagnosis and treatment generally yield a good prognosis.

1. Definition and Etiologies

Pseudotumor cerebri (PTC) is a syndrome of intracranial hypertension without enlarged ventricles, mass lesion, or any other structural cause. It most frequently occurs in obese women of childbearing age and may also occur in pre-pubescent children.[1] Epidemiologic studies performed in the 1980s determined that the incidence in the general population is 0.9 per 100 000 people, rising to 19 per 100 000 in obese women of childbearing age.[2] However, with the rise in obesity in recent decades, newer studies have shown that the incidence of PTC may have doubled over the past 20 years.[3,4] The most common form of the disorder is termed idiopathic intracranial hypertension (IIH). However, a secondary cause is sometimes identified that produces the identical clinical syndrome.

Medications commonly used in dermatologic practice are associated with PTC, including retinoids, tetracyclines and corticosteroids. These medications are often used in a population that may be fundamentally more prone to develop PTC, i.e. young women who are being treated for acne. PTC should be suspected in any patient who develops symptoms of intracranial hypertension while taking such medications, including children, men and non-obese women. Its major morbidity is permanent visual loss that is sometimes severe.[5] It is important to recognize medication-induced PTC, as discontinuation of the medication often results in resolution of the condition.

The nomenclature in the medical literature for this disorder has evolved over the years and is somewhat confusing. The old terminology of 'benign' intracranial hypertension has been abandoned, as the complications are not at all benign. For the purposes of this article, the term 'IIH' is reserved for patients with the idiopathic form. 'PTC' and 'intracranial hypertension' are more inclusive terms, and will be used for the discussion of medication-induced intracranial hypertension.

Table I. Diagnostic criteria for pseudotumor cerebri syndrome

If symptoms are present, they may only reflect those of generalized intracranial hypertension or papilledema
If signs are present, they may only reflect those of generalized intracranial hypertension or papilledema
Documented elevated CSF pressure measured by lumbar puncture in the lateral decubitus position
Normal CSF composition
No evidence of hydrocephalus, mass, structural or vascular lesion on MRI or contrast-enhanced CT scan for typical patients, and MRI and MR venography for all others
If no other etiology is identified, the disorder is termed idiopathic intracranial hypertension

CSF = cerebrospinal fluid; **CT** = computed tomography; **MR** = magnetic resonance; **MRI** = magnetic resonance imaging.

Table II. Medications associated with intracranial hypertension

Corticosteroids
Growth hormone
Leuprorelin (LHRH analog)
Levothyroxine sodium (in children)
Lithium
Nalidixic acid
Levonorgestrel implants
Sulfa antibacterials
Tetracyclines
tetracycline
minocycline
doxycycline
Vitamin A (retinol)
vitamin A supplements
isotretinoin
all-*trans*-retinoic acid

LHRH = luteinizing hormone-releasing hormone.

2. Diagnosis

The diagnostic criteria for PTC are listed in table I.[6] PTC is diagnosed by physical examination, neuroimaging and a lumbar puncture. Papilledema is virtually always present and may be asymmetrical (see section 2.2). Magnetic resonance imaging or computed tomography scanning of the brain reveals no hydrocephalus, mass lesion or abnormal enhancement. An empty sella or dilated optic nerve sheaths may be present, both resulting from increased intracranial pressure.[7] After ensuring that there is no intracranial mass, a lumbar puncture should be performed. An opening pressure of at least 250 mm H_2O is required for the diagnosis. Opening pressures of 200–249 mm H_2O are indeterminate. The spinal fluid analysis should reveal normal spinal fluid without evidence of infection, inflammation or malignancy. Magnetic resonance venography is recommended for non-obese women, children and men, in order to exclude a cerebral venous thrombosis.[8] Investigating for a secondary cause includes questioning the patient about medication usage (table II), examination for underlying systemic conditions (table III), complete blood count and a serum vitamin A (retinol) level.[9-11]

2.1 Symptoms

PTC should be suspected when patients complain of headaches or visual disturbances. Headaches occur in 90% of patients with PTC and may be newly acquired or different from the patient's 'usual' headache disorder.[12] The most common description of headache is a frontal pressure but it may have migrainous features,

such as throbbing, photosensitivity, nausea and vomiting. The headaches may be constant or intermittent.[13]

The visual disturbances of PTC are varied. The most frequent and often the earliest manifestations are transient obscurations of vision (TOV). TOV are fairly specific indicators of papilledema but do not predict the severity of optic nerve swelling or the degree of visual loss.[5,14,15] In fact, patients may complain of TOV and have normal visual function. The typical description of TOV is transient blurring or complete loss of vision ('black out' or 'gray-out') in one or both eyes, lasting seconds. It is often produced when the patient bends over or rolls their eyes.

Other patients notice spots, or scotomata, in their vision. The first manifestation of visual loss in PTC is enlargement of the physiologic blind spot. Thus, patients often observe a dark spot in their temporal visual field. It is sometimes described as seeing a shadow in the peripheral vision: "but when I look toward it, there's nothing there". Papilledema usually spares the central visual field in the early stages, so visual acuity is generally not affected early in the course of PTC. However, a small percentage of patients have an aggressive course with rapid visual deterioration and early central visual acuity loss. Chronic papilledema may produce visual field constriction and other visual field defects. The visual loss of PTC is sometimes irreversible and it is a potentially blinding disorder.[5,13] Less frequently reported symptoms include diplopia, tinnitus (may be pulse-synchronous), neck or back pain, and radicular pain.[13,15]

2.2 Signs

The most important sign for diagnosing PTC is papilledema (figure 1, figure 2, and figure 3). Fully developed papilledema may be observed with the direct ophthalmoscope. The borders of the optic nerve head become indistinguishable from the surrounding retina and there is obscuration of blood vessels that cross the optic disc margin. Papilledema is difficult to detect in the early stages, when it may be mild and not apparent using direct ophthalmoscopy that provides a 2-dimensional view of the optic nerve head. Stereoscopic evaluation of the optic discs may be necessary, requiring special equipment and ophthalmic expertise. PTC without papilledema has been described but it is uncommon.[16] However, in the acute phase, it is possible for symptoms to precede the development of papilledma. If there is any suspicion of increased intracranial pressure, prompt evaluation by an ophthalmologist, neuro-ophthalmologist or neurologist is essential.

Table III. Medical conditions associated with intracranial hypertension

Obstruction to cerebral venous drainage
Cerebral venous sinus thrombosis
Dural arteriovenous malformation
Jugular vein obstruction
Systemic illnesses
Iron deficiency anemia
Polycystic ovary syndrome
Sleep apnea
Turner syndrome
Endocrine disorders
Addison disease
Hypoparathyroidism
Obesity, recent weight gain
Orthostatic edema

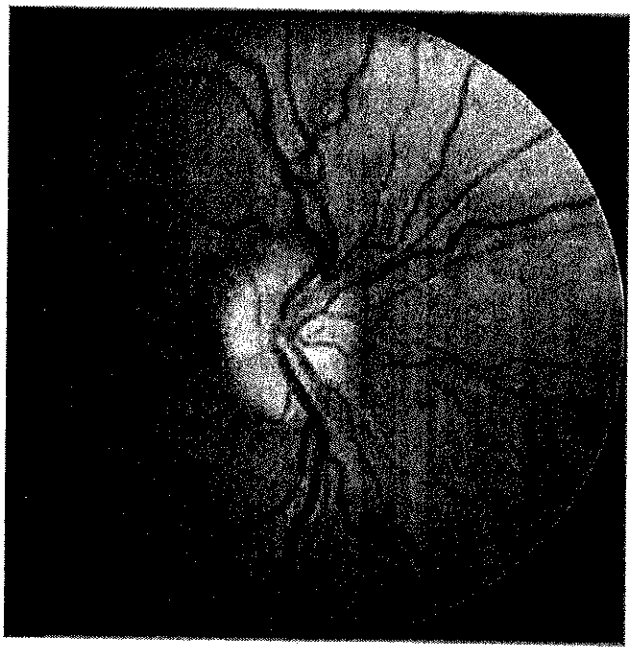

Fig. 1. Moderate (grade 3), chronic papilledema in a young woman with idiopathic intracranial hypertension. There is diffuse optic nerve swelling and a peripapillary halo. All retinal vessels are seen crossing the disc margins.

3. Retinoids

Numerous medications have been implicated in the development of PTC (table II). The association between vitamin A and intracranial hypertension has been known for hundreds of years. A group of Dutchmen visiting Nova Zembla in the Arctic Ocean developed headaches, dizziness, vomiting and dermatitis after ingesting polar bear liver, which was later verified and ascribed to vitamin A toxicity.[17] Subsequently, intracranial hypertension has been described with both naturally occurring and synthetic retinoid usage (table IV).

The action of retinoids is mediated through binding of nuclear retinoid receptors.[18] They affect DNA transcription, similar to hormones.

3.1 Vitamin A (Retinol)

The syndrome of hypervitaminosis A includes dryness, roughness and desquamation of the skin, alopecia, hypomenorrhea, hepatomegaly, splenomegaly and migratory arthralgias.[19,20] The dry eye syndrome, conjunctivitis, cutaneous photosensitivity, contact lens intolerance, refractive changes, corneal opacities and abnormal retinal function are ocular manifestations of vitamin A toxicity.[21] Intracranial hypertension occurs in 50% of cases of hypervitaminosis A, and was first reported in 1954 in children and adults.[22-24] The neurologic symptoms are headache, diplopia, pulsatile tinnitus, TOV and visual loss. Psychosis is uncommon.[25] Most of the reported cases occurred in patients taking vitamin A for acne vulgaris.[22,26-29] Excessive dietary intake from fish liver oil,[30] shark liver,[31] vitamin-fortified milk,[32] and carrots[33] may also cause intracranial hypertension, which has been dubbed 'liver lover's headache'.[34] One patient with a history of IIH developed recurrent signs and symptoms of increased cerebrospinal fluid (CSF) pressure when she overindulged on carrots as part of her prescribed weight loss regimen.[33]

Dietary sources of vitamin A include preformed vitamin A (derived from animal sources) and dietary carotenoids (from oils, fruits and vegetables). Preformed vitamin A is absorbed following the processing of retinyl esters in the small intestine with a high efficiency of absorption (70–90%). As the amount of preformed vitamin A increases, its absorbability becomes nonsaturable and remains high.[35] β-Carotene has a much smaller absorption efficiency (<25%) which decreases as dietary intake increases. β-Carotene must be converted to vitamin A for absorption in the intestine, and the bioavailability of β-carotene varies with processing methods and among different types of foods. Hence, vitamin A toxicity is most likely to arise following pharmaceutical supplementation of vitamin A or by ingesting an animal derived food source. Because of the inconsistent bioavailability from orally ingested sources, the standard of reference for nutritional requirements has been changed from an international unit (IU) system to a retinol activity equivalent (RAE) system. One RAE is equivalent to 1μg of all-*trans* retinol, 2μg of supplemental all-*trans* β-carotene, 12μg of dietary all-*trans* β-carotene or 24μg of other dietary provitamin A carotenoids. An alternate system (table V) uses retinol equivalents (RE), where one RE equals 1μg of all-*trans* retinol, 2μg of supplemental all-*trans* β-carotene, 6μg of dietary all-*trans* β-carotene or 12μg of other dietary provitamin A carotenoids. Since many products are still labeled in the IU system, the recommended dietary guidelines in table V are provided using both measurement systems where values were available.[35] Dietary sources that are rich in vitamin A include fish, eggs, carrots, sweet potatoes, leafy greens, broccoli, red bell peppers, tomatoes, apricots and cantaloupe. Doses of 40 000–600 000 units/day are usually implicated in vitamin A toxicity. Infants, children and adults may be affected.[36,37] Serum vitamin A levels are elevated and the syndrome reverses after the source of vitamin A is discontinued. However, some patients require additional therapy to lower their intracranial pressure as the vitamin A level

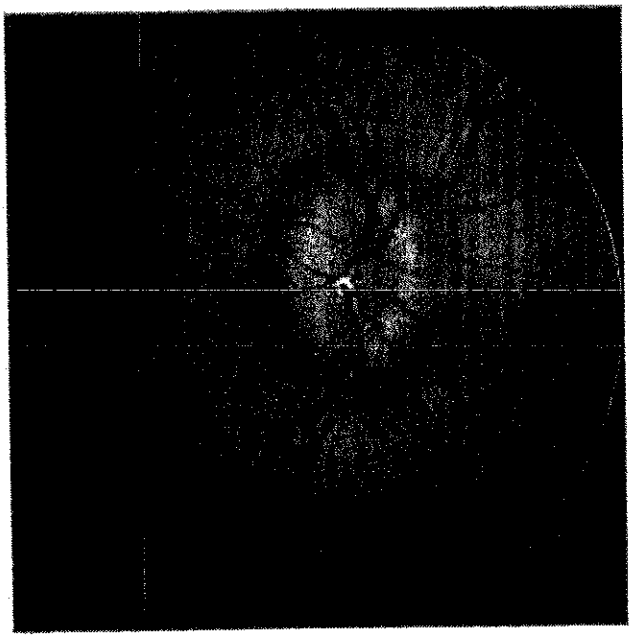

Fig. 2. Moderate (grade 4), subacute papilledema. The optic disc is elevated 360° and there is a peripapillary halo. Because of increased vascularity in the acute and subacute stages, the optic disc appears redder ('hyperemic') than in figure 1.

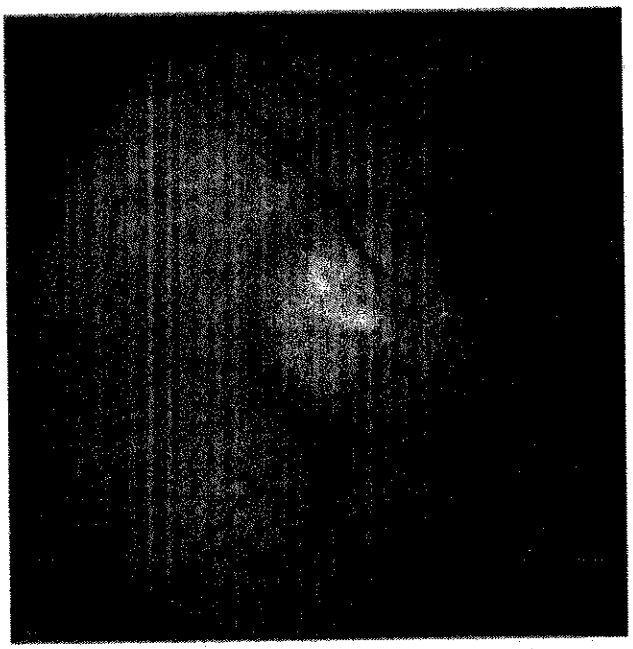

Fig. 3. Severe (grade 5) papilledema. The optic nerve is diffusely swollen. Segments of the major arterioles and veins are obscured by the swollen nerve fiber layer as they cross the disc margin.

Table IV. Dermatologic conditions treated with systemic retinoids

Acneiform disorders
Acne vulgaris
Rosacea
Morbihan disease
Hidradenitis suppurativa
Gram-negative folliculitis
Disorders of cornification
Psoriasis (psoriasis vulgaris, pustular psoriasis, erythrodermic psoriasis)
Ichthyosis
Keratodermas (symmetrical progressive erythrokeratoderma)
Papillon-Lefevre syndrome (epidermolytic hyperkeratosis)
Inflammatory and immunodermatosis
Atrophoderma vermiculatum
Lupus erythematosis
Lichen planus
Sarcoidosis
Granuloma annulare
Disorders of epidermal differentiation
Epidermodysplasia verruciformis
Confluent and reticulated papillomatosis
Axillary granular parakeratosis
Neoplasia
Sebaceous hyperplasia
Lesions of Muir-Torre syndrome
Leukoplakia
Recurrent condylomata accuminata
Langerhans cell histiocytosis
Follicular mucinosis
Cutaneous T-cell lymphoma
HIV-associated dermatoses
Papular mucinosis
Eosinophilic folliculitis
Pediatric dermatologic disorders
Acne vulgaris
Lamellar ichthyosis
Nonbullous congenital ichthyosiform erythroderma
Harlequin ichthyosis
Palmoplantar keratoderma/keratitis, ichthyosis and deafness (KID) syndrome
Severe pityriasis rubra pilaris
Severe Darier disease
Extensive, recalcitrant pustular or erythrodermic psoriasis
Xeroderma pigmentosa
Nevoid basal cell carcinoma syndrome

gradually returns to normal. A double-blind, randomized, placebo-controlled trial of three sequential doses of 25 000IU of vitamin A compared with placebo in infants showed a higher incidence of bulging fontanelle in the vitamin A group.[38] The response was dose related and cumulative, occurring only after the second and third doses. Interestingly, intracranial hypertension has also been described with hypovitaminosis A in an infant with multiple vitamin deficiencies.[39] The CSF pressure normalized after 2 months of parenteral vitamin A therapy.

The association between vitamin A and intracranial hypertension is so strong that vitamin A levels were studied in the serum and CSF of patients with IIH who had no excessive or supplementary intake of vitamin A. One study showed significantly elevated serum retinal concentrations in IIH patients compared with control subjects,[40] while another study showed a non-statistically significant elevation in IIH patients.[10] Retinol binding protein was elevated in 25% of IIH patients and none of the controls,[10] while retinyl ester concentration was similar in the two groups.[40] Some IIH patients demonstrated significantly higher CSF levels of vitamin A than non-IIH controls, although the median retinal level was similar to controls with normal and elevated intracranial pressure.[11] The mechanism of the association is uncertain, but an effect of retinal on CSF absorption is postulated.[11,41]

3.2 Isotretinoin

3.2.1 Indications, Dosage, and Pharmacokinetics

Isotretinoin is reserved for the treatment of severe, recalcitrant nodular acne and has also shown effectiveness in the treatment of psoriasis and other disorders of keratinization (table II). It is a retinoid that inhibits sebaceous gland function and keratinization through an unknown mechanism. After 3–4 months of therapy there is an alteration of skin lipid composition, a marked reduction in sebaceous gland size and decreased sebum production.[42] Isotretinoin is more effective in reducing sebum production, and in treating acne in general, than either vitamin A or etretinate.[43] The usual dose is 0.5–2.0 mg/kg/day for 15–20 weeks. Linear pharmacokinetics were demonstrated in healthy men, with peak plasma concentrations measured 3–4 hours after administration and a half-life of 1.3–2.4 hours.[44] Isotretinoin is metabolized into four major metabolites and then eliminated. The two main metabolites are 13-*cis*-retinoic acid and all-*trans*-retinoic acid (ATRA). Intracranial hypertension has been reported with therapeutic administration of both metabolites. Other ocular adverse effects of isotretinoin include dry eye syndrome (and subsequent contact lens intolerance or altered refraction), photosensitivity and anterior segment inflammation.[45,46]

3.2.2 Pseudotumor cerebri (PTC) and Isotretinoin

Headache was the most common adverse effect from isotretinoin use in a report from the US Adverse Reaction Reporting

System from 1982 to 1985, accounting for 15 of 104 spontaneously reported adverse events.[47] Four cases of headache were attributed to IIH.[48,49] Some patients were taking isotretinoin and tetracyclines simultaneously, suggesting a synergistic action between the two agents.[48,49]

A physician reporting system identified 181 cases of intracranial hypertension associated with isotretinoin. The mean time from exposure to the onset of symptoms was 2.3 months. Twenty-four percent of patients took a tetracycline just before, or simultaneously with, starting isotretinoin. After discontinuing the isotretinoin, six patients had recurrent signs and symptoms of PTC when re-challenged with isotretinoin.[50]

3.3 Etretinate/Acitretin

3.3.1 Indications, Dosage and Pharmacokinetics

Etretinate (13-*cis*-retinoic acid) was synthesized almost two decades after isotretinoin. It is the drug of choice for treating generalized pustular psoriasis, although prolonged remissions are not as frequent as with isotretinoin for acne.[43] After oral administration, it is hydrolyzed to acitretin.[18] Etretinate enjoyed long-term usage in Europe before being introduced into the US. It may remain in fatty tissues for over 2 years.[51] Since acitretin is less lipophilic than etretinate and considered to pose a shorter duration of potential teratogenicity, it replaced etretinate (withdrawn from the Canadian market in 1996 and the US market in 1998). The concurrent ingestion of ethanol with acitretin metabolizes it back to etretinate, which potentially increases the teratogenic risk. Acitretin is indicated for the treatment of severe psoriasis, including the erythrodermic and generalized pustular types, in adults. The initial dosage is 10–25mg daily and is gradually increased until a response is obtained.

3.3.2 PTC and Etretinate

There are no proven cases of intracranial hypertension reported with etretinate use. One 75-year-old patient developed severe headaches and other systemic symptoms after treatment of mycosis fungoides with etretinate.[52] Papilledema was observed and the patient probably had intracranial hypertension, but a diagnostic lumbar puncture was not performed. Another report described two other patients with symptoms ascribed to intracranial hypertension from etretinate. Neither patient had papilledema nor confirmation of elevated CSF pressure with a lumbar puncture. One was a 67-year-old woman who was treated for mycosis fungoides. She experienced headache and vomiting, associated with fever, heart block, hypertension and renal insufficiency.[53] Another patient developed severe headaches after the dose of etretinate was reduced from 1.0 to 0.7 mg/kg in successfully treated Darier disease.[53] Her symptoms resolved when etretinate was discontinued, but recurred months later after taking natural vitamin A. Headache is a known adverse effect of retinoid therapy; the diagnosis of intracranial hypertension in these two patients is unsubstantiated.

Table V. Recommended dietary intake of vitamin A[3]

Age (y)	DRI (μg)	UL	RDA (IU)
1–3	300	600	NS
4–8	400	900	2500
Females 9–13	600	1700	NS
Females >14	700	3000	5000
Pregnancy	770	3000	NS
Lactating women	1300	3000	NS
Males 9–13	600	1700	NS
Males >14	900	3000	4000

DRI = dietary reference intakes (retinol equivalents); **IU** = international units; **NS** = not specified; **RDA** = US recommended daily allowance; **UL** = tolerable upper intake level.

3.4 PTC and Tretinoin

ATRA, the primary metabolite of isotretinoin, is used primarily for the treatment of leukemias, and most reports of intracranial hypertension are associated with its use in acute promyelocytic leukemia.[54-60] ATRA induces differentiation and decreased proliferation of promyelocytic leukemic cells, but its mechanism of action is unknown. The recommended dosage of ATRA is 45 mg/m^2/day administered orally until remission, up to a maximum course of 90 days. Between 20% and 50% of patients experience the 'retinoic acid syndrome', characterized by fever, fluid retention, pulmonary infiltrates, pleural and pericardial effusions, dyspnea and weight gain, with or without leukocytosis.[61] The syndrome can be fatal but is usually successfully treated with corticosteroids.

4. Tetracyclines

4.1 Indications, Dosage, Pharmacokinetics

The tetracyclines are structurally similar compounds that inhibit bacterial protein synthesis. Minocycline and doxycycline are more lipophilic than other tetracyclines, are better absorbed in the gastrointestinal tract, and pass through the outer cell membrane easily. After gastrointestinal absorption, an energy-dependent active transport system pumps tetracyclines through the bacterial cytoplasmic cell membrane.[62]

The tetracyclines have broad-spectrum activity against Gram-positive and Gram-negative bacteria. Various mechanisms are postulated to explain their effectiveness in the treatment of acne vulgaris. A direct bactericidal effect may inhibit *Propionibacterium acnes* in the sebaceous follicles from metabolizing lipids into free fatty acids.[62] *P. acnes* begins the inflammatory cascade by

producing neutrophil chemotactic factors.[61,63] When neutrophils reach the inflamed site, they release inflammatory mediators, including lysosomal enzymes and reactive oxygen species. Jain et al.[63] found that tetracycline decreased neutrophil chemotactic factor production by 35% and inhibited the release of reactive oxygen species *in vitro*. The effect of tetracycline and minocycline on complement activation is probably not involved in the inflammatory response of *P. acnes*.[64]

4.2 Intracranial Hypertension and Tetracyclines

Most of the reported cases of PTC are related to the use of tetracyclines for the treatment of acne vulgaris. Tetracycline, minocycline and doxycycline have been implicated.

4.2.1 Tetracycline

Tetracycline is associated with PTC in patients of all ages.[65-76] Tetracycline-induced PTC is commonly observed in children and adolescents because of its use for acne treatment, but it can also occur in infants. Symptoms may develop within hours to days of beginning tetracycline therapy but often take several months to manifest.[67,68] Most patients have improvement after stopping the antibacterial, and rechallenge may reproduce the syndrome. There may be a genetic susceptibility to the development of intracranial hypertension with tetracycline, as it has been reported among family members.[67]

4.2.2 Minocycline

Almost all cases of minocycline-associated PTC occur in teenagers and young adults being treated for acne.[77-80] There is a high proportion of females in this group. The onset of symptoms is generally ≤8 weeks after beginning minocycline treatment. Occasionally, delayed onset occurs after taking the medication for ≥1 year.[77-79] There may be concomitant use of vitamin A supplementation.[77] The syndrome generally resolves after the minocycline is discontinued and medical treatment is initiated, with minimal, or no, visual loss.

4.2.3 Doxycycline

The association between doxycycline and PTC is the least well established of all the tetracyclines. Two cases were reported in patients taking doxycycline for malaria prophylaxis.[81] One case is documented in the Swedish literature.[82] A recent query to the membership of the North American Neuro-Ophthalmology Society revealed seven new cases.[83] Three of the seven developed symptoms of increased intracranial pressure within weeks of starting doxycycline, and five patients experienced permanent visual deficits. The small number of cases may either reflect relatively infrequent usage of doxycycline for acne compared with tetracycline or minocycline, or a decreased propensity for doxycycline to produce increased intracranial pressure.

5. Corticosteroids

Corticosteroids are used to treat PTC and are incorporated when the patient experiences rapid visual decline as a temporizing agent prior to a definitive surgical procedure. They reduce intracranial pressure caused by cytotoxic edema. It seems somewhat contradictory that they are also associated with the development of PTC. PTC usually develops when the corticosteroids are withdrawn for the treatment of an unrelated systemic condition.[75,84-86] Gradual withdrawal of corticosteroids with or without acetazolamide administration has been successfully employed to prevent intracranial hypertension.

6. Hormone Therapy

Hormone therapy is sometimes incorporated into the management of acne in young women. There are a few reports of PTC occurring with oral contraceptive use but the association has never been borne out in case-control studies of PTC.[1,12] Given the large number of women using oral contraceptives, a direct relationship is unlikely. It is possible that hormone-related weight gain or fluid retention may be contributory in the reported patients. Alternatively, there may be an underlying cerebral venous thrombosis that is associated with oral contraceptive use. In contrast to oral contraceptives, there is a well established relationship between PTC and levonorgestrel-releasing implants.[87-89] Headache is a common adverse effect of levonorgestrel; patients developing headaches or visual disturbances while using it should be evaluated for funduscopic evidence of PTC.

7. Conclusions and Recommendations

PTC is an important diagnostic consideration for patients who develop headaches or visual disturbances while taking retinoids, tetracyclines and corticosteroids for dermatologic disorders. Children and teenagers are most frequently affected. If PTC is suspected, patients should be promptly evaluated by an ophthalmologist or neurologist. All patients with papilledema should be investigated with brain neuroimaging and a lumbar puncture, and managed by a neurologist or neuro-ophthalmologist who is familiar with the condition.

Early papilledema may be difficult to discern using the handheld direct ophthalmoscope, and stereoscopic viewing by an ophthalmologist may be necessary. The potentially causative medication should be discontinued as soon as PTC is suspected and during the evaluation process. Besides terminating the agent if the patient has PTC, patients should avoid taking medications in the same class of agents (e.g. other tetracyclines). Other dermatologic treatments known to produce PTC are not recommended as an alternative treatment, as some people seem to be susceptible to the disorder for unknown reasons. Vigilant questioning of the patient at follow-up visits for the development of headaches (or change in

the usual pattern of a pre-existing headache) or new visual symptoms is recommended, as the key to a successful outcome is a high index of suspicion and early detection.

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